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### RECOMMENDATIONS FOR STANDARDIZATION AND PHENOTYPE DEFINITIONS IN GENETIC STUDIES OF OSTEOARTHRITIS: THE TREAT-OA CONSORTIUM

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**Purpose:** The objective of this study is to examine heterogeneity among clinical/symptomatic and radiographic osteoarthritis (COA/ROA) phenotypes. The need for standardization of OA phenotypes in epidemiological studies is addressed.
**Methods:** We collected descriptions of all OA phenotypes within the 28 studies involved in the TREAT-OA consortium. There are 18 cohort studies, 9 case-control studies and 1 randomized-controlled trial.
To discover if differences in OA definitions result in different association results, we created all hip OA definitions used by studies of the consortium in the Rotterdam Study-I. Association analyses were performed to study the relationship between different OA definitions of the hip and age, gender and (BMI) using one-way ANOVA.
After consensus was reached for the definition of knee and hip ROA, each study standardized its ROA phenotype definitions and the prevalence of ROA of the knee and hip was compared before and after standardization for 6 cohort studies.
**Results:** A total of 54% (15/28) of studies defined OA according to radiographic features, while 46% (13/28) used a clinical or clinical + radiographic OA definition. All studies with COA (n=11) used a different definition and/or assessment of OA status for COA of the knee (n=10), hip (n=8) and hand (n=2). For knee, hip and hand ROA, 5, 4 and 6 different ROA definitions were used respectively.
When hip OA was defined as one definite osteophyte, subjects with hip OA were significantly more frequent men compared to controls (P=2×10E10), whilst total hip replacement cases were more frequent women compared to controls (P=1×10E4). If ROA definitions are compared, we observed that hip ROA defined as definite JSN and one definite osteophyte was not associated with BMI (p=0.94), whilst hip OA cases defined as only one definite osteophyte were associated with a slightly lower BMI (p=0.049).
After standardization, the prevalence of hip- and knee ROA was similar in 6 cohort studies. Standardization of clinical OA phenotypes, although desirable, was not possible due to the case-control study design of the studies.
**Conclusions:** 1. Phenotype definitions do influence the outcomes in association studies and therefore ROA phenotypes within the TREAT-OA consortium were standardized to reduce heterogeneity. A standardized ROA phenotype definition will improve the power in the anticipated genetics studies.
2. Additional research is needed to reach a consensus for definitions of clinical/symptomatic OA. We suggest that more thought should be given to the establishment of clear guidelines for future research using clinical/symptomatic OA cohorts, as this would have implications not just for genetic studies, but also for the assessment of biomarkers, imaging and interventional studies.
3. In the future, more precise OA phenotypes and stratification according to phenotypes should be mandatory for inclusion in large meta-analyses.

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### THE COSTS ASSOCIATED WITH CHRONIC KNEE PAIN AND KNEE OSTEOARHTRITIS - A POPULATION-BASED STUDY FROM SWEDEN

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**Purpose:** To identify the costs associated with knee OA in an elderly Swedish population, from a societal perspective.
**Methods:** A questionnaire about knee pain was sent to 10,000 participants (age range 56-84 years) from the population-based Malmö Diet and Cancer cohort (responders: 7,736). A random sample of 1,300 subjects with chronic knee pain (duration of at least one month in the last year) and a control group (650 subjects) were invited to a clinical examination including x-ray of both knees (998 + 487 subjects underwent examination and x-ray). Subjects who fulfilled ACR criteria and/or had radiographic knee OA (ROA) were considered to have knee OA. The direct costs estimated were hospitalizations, visits to nurse/GP, physiotherapist or knee specialist, call to nurse/GP, and drugs, due to knee pain. The indirect costs estimated were sick-leave and pre-retirement, due to knee pain.
**Results:** Approximately 20% (1,605/7,736) of the subjects had chronic knee pain. Of those that participated in the examination and x-ray, 50% (502/998) had knee OA. Among subjects with knee OA and chronic knee pain; 39% had direct costs and 4% indirect costs, as compared to 20% and 1.6%, respectively, among subjects with chronic knee pain, but no knee OA, and 3% and 0%, respectively, among control subjects. The mean total yearly cost (direct + indirect) per subject with knee OA and chronic knee pain was €1,715. The major contributor (71%) was indirect costs (sick-leave and pre-retirement). The total costs for the subjects who fulfilled ACR criteria were approximately 70% higher than for those who had ROA (€2,060 vs. €1,189). Both females and males of age <65 years or age 65≥ with knee OA and chronic knee pain had significantly higher total costs than subjects of the same sex and age group with chronic knee pain, but no knee OA. Females of age <65 years with knee OA, or with chronic knee pain but no knee OA, had significantly higher total costs than females of age 65≥ in the same diagnostic group. A similar significant age dependence was not seen in males.
**Conclusions:** A large proportion (50%) of the subjects with chronic knee pain had knee OA. Total costs were markedly dependent on diagnostic group, age and sex. The major contributor (71%) was indirect costs driven by 4% of the subjects. If the prevalence rates and costs from this study could be extrapolated to the general 56-84 year old population in Sweden, this would correspond to approximately 260 000 Swedish individuals with chronic knee pain and knee OA and a total annual cost of €560 millions.

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### WOMAC TOTAL SCORE IS ASSOCIATED WITH COSTS IN SUBJECTS WITH CHRONIC KNEE PAIN WITH OR WITHOUT OSTEOARTHRITIS

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**Purpose:** To evaluate the influence of WOMAC total score on direct and indirect costs associated with chronic knee pain, with or without a diagnosis for osteoarthritis, in an elderly Swedish population.
**Methods:** A random sample of subjects with self-assessed chronic knee pain (duration for at least one month in the last year) was drawn from the population-based Malmö Diet and Cancer cohort. After clinical examination, including X-ray, subjects were divided into two diagnostic groups:
"OA" (n=502): Subjects with chronic knee pain fulfilling ACR criteria and/or having a radiographic diagnosis of osteoarthritis.
"Pain" (n=496): Subjects with chronic knee pain but no diagnosis of osteoarthritis.
For each subject, sex, age, body mass index (BMI) and WOMAC total score were assessed, and the total yearly costs per patient estimated. Total costs included direct costs (hospitalizations, visits to GP/knee specialist/nurse/physiotherapist and medications due to knee pain) and indirect costs (sick-leave and pre-retirement). The quantitative influence on total costs from the WOMAC total score, and from the demographic variables, was

studied using a "2-part model", where the probability of non-zero total costs is modelled by logistic regression, and the mean level of the logarithm of non-zero total costs by a general linear model (GLM). The diagnostic group was a factor in both models, and the potential predictors including WOMAC total score, sex, age and BMI were integrated as covariates.
**Results:** Of the 998 subjects included, 331 were male and 667 females. Age ranged from 56 to 84 (mean 69.2) years, BMI from 14.4 to 56.0 (mean 28.1) kg/m$^2$, and WOMAC total score from 0 to 94 (mean 31.3) units. Based on the 2-part model, the probability of non-zero total costs was 0.406 in the OA group and 0.210 in the pain group. WOMAC total score, as a continous variable, was a statistically significant ($p<0.0001$) predictor of the probability for non-zero total costs, and also a statistically significant predictor ($p=0.0082$) of the mean level of non-zero total costs (€4,955 "OA" and €2,819 for "pain" group). An increase in WOMAC total score of 30 units was estimated to correspond to an odds ratio of 2.05 (95% CI 1.62 to 2.61) regarding the probability of non-zero total costs, and a multiplier of 1.52 (95% CI 1.12 to 2.07) regarding the mean level of non-zero total costs. Age 65≥ was associated with statistically significantly ($p<0.001$) lower mean non-zero total costs, compared with age <65 years (multiplier = 0.42). An explanation for this is that pre-retirements costs, which are likely to constitute a very large part of total costs, only occur at age <65 years.
**Conclusions:** The mean total costs increased significantly with the WOMAC total score, as do the probability of reporting non-zero total costs and the mean non-zero total costs, both of which are constituent factors of the mean total costs. Higher disease activity, as reflected by higher WOMAC score, correlates with higher costs.

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### CAN WE EXPLAIN THE DRAMATIC INCREASE IN TKR UTILIZATION RATES IN US BY POPULATION SIZE AND OBESITY EPIDEMIC GROWTH?

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**Purpose:** Utilization of total knee replacement doubled over the decade between 1997 and 2007. Several published studies attributed these increases to the growing population and the obesity epidemic, although the most recent published data suggest the proportion of obese Americans increased by < 15% between 1997 and 2007. We sought to investigate whether TKR rate increases were disproportionally higher in younger compared to older age groups.
**Methods:** We used data from National Inpatient Sample (NIS), the largest all-payer inpatient care database in the United States, containing data from approximately 8 million hospital stays each year. NIS data are designed to examine trends in utilization of specific procedures over time. We coupled the NIS-based data with population size estimates from US Census data to estimate changes in TKR utilization rates over the decade from 1997 to 2007 stratified by age groups (18-44, 45-64, 65-84, 85+). We estimated the proportion of TKRs performed in each age group across ten year period and compared rate of change in TKR utilization with changes in population size from 1997 to 2007.
**Results:** In 2007 550,161 total knee replacements were performed in the US, 100% more than were performed in 1997. During the same time period the overall population size increased by just 15%. While the population of 45-64 year olds grew by 38%, the number of TKRs done in this age group more than tripled (Figure 1). The largest increase in population over the decade (41%) was observed in 85+ age group. The corresponding increase in TKR utilization in this age group reached 70%. Across all age groups the increase in TKR rates was substantially higher than corresponding increase in population size, but relative difference between the growth in population and utilization of TKR was highest in 44-65 age group. TKRs in the younger age group 45-64 increased from 25% of all TKRs performed in 1997 to 40% in 2007. In contrast, in 1997 69% of all TKRs were done in persons 65-84 years of age compared to only 55% of all TKRs done in the 2007. The proportion of TKRs performed in oldest age group 85+ years of age decreased slightly from 3.5% in 1997 to 2.9% in 2007. Examination of population size trends and trends in the obesity epidemic suggested that only about 20% of increases in utilization of TKRs could be explained by population and obesity growth.
**Conclusions:** The absolute number of TKRs increased in all age groups during the decade from 1997 to 2007. As a proportion of all TKRs performed in a particular year, the proportion performed in younger age groups increased and proportion of TKRs done in older persons decreased over the ten year period. These data suggest that expanding the indications for TKR in younger ages is the likely explanation for the dramatic increase in TKR rates in US.

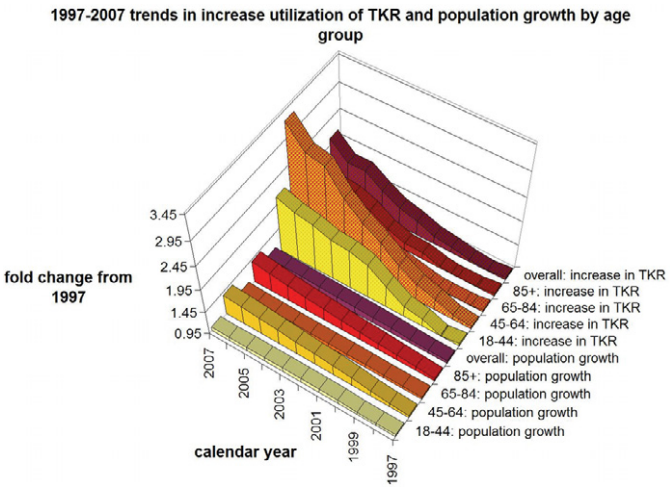

Figure 1

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### AFRICAN-AMERICAN AND WHITE DIFFERENCES IN KNEE PAIN AND ARTHRITIS IMPAIRMENT: A POPULATION-BASED STUDY

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**Purpose:** Studies suggest that some minority groups, especially African-Americans with osteoarthritis, may be at risk for higher rates of lower extremity pain and disability compared to Caucasian Americans. In addition, African-Americans are less likely to undergo arthroplasty compared to Caucasian Americans. However, more research needs to be done to assess possible differences in lower extremity pain and arthritis impairment among minorities and Caucasian Americans.
**Methods:** The following study tests the null hypothesis that the association between right knee pain and arthritis impairment does not differ between African-Americans and Caucasian Americans, after adjusting for other possible predictor variables, such as gender, age, and household income. The findings from the population-based 1998 National Health Interview Survey (N=30,534 adults) were used. Descriptive and correlational procedures evaluated possible Black/White differences in the association between right knee pain and arthritis impairment related to walking ¼ of a mile without special equipment.
**Results:** The null hypothesis was mostly rejected. The association between right knee pain and arthritis impairment was higher among African-Americans ($r=+0.206$, N=466, $p<0.000$) than among whites ($r=+0.127$, N=2,579, $p<0.000$). These results remained significant after adjusting for possible intervening variables.
**Conclusions:** These findings highlight the need to screen for and aggressively manage knee pain and arthritis impairment, especially among African-Americans.

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### OSTEOARTHRITIS (OA) IN YOUNG PATIENTS DUE TO SPORT KNEE INJURY

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**Purpose:** To know Knee OA prevalence in young patients with anterior cruciate ligament (ACL) injury and evaluate risk factor for OA severity.
**Methods:** A retrospective and descriptive study. Inclusion criteria, patients with anterior cruciate ligament injury who underwent to arthroscopic ACL repair. OA was documented at surgery moment by the surgeons. We recollect variables as risk factor in development knee OA in young patents: presence of meniscal lesion, gender, age, weight, evolution time, mechanism of injury. Statistical analysis was done with STATA software®. A descriptive analysis, bivariated analysis was realized with appropriated parametric statistical test.